FRIGID ZONE **MEDICINE**
Review • DOI: 10.2478/fzm-2021-0008

Mammalian hibernation: a unique model for medical research

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Abstract

Hibernation is an adaptive behavior for some small animals to survive cold winter. Hibernating mammals usually down-regulate their body temperature from ~37°C to only a few degrees. During the evolution, mammalian hibernators have inherited unique strategies to survive extreme conditions that may lead to disease or death in humans and other non-hibernators. Hibernating mammals can not only tolerant deep hypothermia, hypoxia and anoxia, but also protect them against osteoporosis, muscle atrophy, heart arrhythmia and ischemia-reperfusion injury. Finding the molecular and regulatory mechanisms underlying these adaptations will provide novel ideas for treating related human diseases.

Keywords

hibernation; deep hypothermia; hypoxia; osteoporosis; muscle atrophy; arrhythmia; ischemia-reperfusion

Received 28 January 2021 accepted 24 April 2021

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Mammalian hibernation is an effective strategy to save energy under adverse conditions. Hibernating mammals are able to regulate body temperature (T_b) between ~37°C and ~0-10°C in winter, exhibiting multiple alternative euthermic and torpid states known as hibernation bouts[1-3]. In the torpid state, the heart and respiration rates drop to 3-10 beats/min and 4-6 breaths/min, respectively, which are less than 1/30 of their normal levels[1-2]. During interbout arousal, mammalian hibernators restore their T_b, heartbeat and respiration within 2-4 hours[3-4]. Hibernation involves multiple extreme factors, which are highly stressful and even lethal for non-hibernating mammals[5-9]. During the evolutionary interaction between hibernators and the environment, a set of evolutionary genetic and functional adaptations enable hibernators to survival these extreme factors or stress conditions. Thus, exploring the mechanisms of hibernation may provide new ideas on medical management of certain diseases.

Neurohumoral regulation of T_b and metabolism

The T_b and metabolism are precisely regulated before and during hibernation. A hypothalamic neuronal circuit has been found to control the initiate and exit of the hypothermic/hypometabolic state in both hibernators[10] and non-hibernators[11-12]. Several compounds have been used to induce a hibernation-like hypothermia in non-hibernators[13-15], suggesting an intriguing possibility that hibernation might be utilized for medical purposes.

Tolerance of hypothermia

Prolonged deep hypothermia can cause irreversible damage of organ functions[5-7, 16], which is a common reason for the failure of organ transplantation. The dog dies from heart arrest or severe ventricular fibrillation during hypothermia near 20°C T_b[17]. Thus, in hypothermic anesthesia, the lowest safe T_b range suggested by the American Heart Association is 28-32°C[18]. In contrast, all hibernators are able to decrease their T_b from ~37°C to near ambient temperature, even freezing point, without irreversible consequences. They keep a typical blood pressure of 90/30 mmHg with a maintained autoregulation of coronary flow even when T_b is near freezing point during hibernation[19].

The hypothermia resistance of hibernators is based on their adaptations at the cellular level. For example, cellular K^+ of aortic strips falls from 147 mM to 138 mM after 48 hours exposure at 7°C in ground squirrels, while from 151 mM to 14 mM in rats[20]. Membrane potentials and excitability are more stable in cardiac cells of hibernators[21]. Even action potentials of 60 mV were recorded in ground squirrel myocardium super-cooled to -5°C[22]. Cardiac myocytes from hibernators also keep a homeostatic intracellular free calcium and a vigorous contractility at 10°C or lower, in contrast

to the development of calcium overload[23] and the loss of contractility[19, 24] below 25°C in non-hibernators[19, 23-25].

Organ preservation

The preservation of living organs under low temperature is a fundamental issue in transplantation. It is found that hibernation-inducing trigger (HIT) obtained from hibernating woodchucks prolonged the survival time of an auto-perfused canine multiorgan preparation, including working heart, lung, kidney, etc., from an average of 16 hours to 43 hours[26]. This study produced one of the longest average survival times for organ preservation. Compare to that of rats, the liver of torpid ground squirrels performs better during cryo-preservation[2].

Endurance of hypoxia

Hibernating hedgehogs were found to survive inhalation of pure nitrogen and different concentrations of carbon dioxide in oxygen for 2 hours before an initial rise of heart rate and a prolongation of QRS duration[27]. Another study shows that 100% non-hibernating ground squirrels survive 1 hour of 4.5% O_2 while 80% rats died[28]. In addition, neural progenitor cells of Arctic ground squirrel were demonstrated to be resistant to oxygen deprivation *ex vivo*[29-30].

Protection against ischemia-reperfusion

Reperfusion after ischemia is another fatal problem for non-hibernating mammals[31-32] because it causes severe and durative damage due to the burst of reactive oxygen species (ROS) and the loss of intracellular calcium homeostasis[33]. During the arousal from hibernation, the onset of non-shivering heat production precedes the rises of heart and respiration rates, resulting in an ischemic/anoxic condition at the early stage of arousal[2]. With increases of heart and respiration rates, all organs are expected to undergo a post-ischemia reperfusion process[2]. As an adaptation, significant less injury of heart tissue was observed in active ground squirrels than in rats during ischemia-reperfusion[34]. The ability to keep ROS homeostasis[35] in hibernating mammals is at least one of the fundamental mechanisms underlying their protection against ischemia-reperfusion.

During ischemia-reperfusion procedure, the heart of ground squirrel also exhibits less ventricular fibrillation and tachycardia than rat heart[34].

Resistance against arrhythmia

During hibernation, the T_b of the hibernators has to pass a critical band around 20°C, where non-hibernating mammals develop severe ventricular fibrillation[17], but fibrillation was never seen in hibernators during the entrance and arousal of hibernation. Even the slight arrhythmia, such as intermittent periods of asystole and bradycardia, were proved to result from strong sympathetic innervation[36].

More importantly, hibernators resist to arrhythmia against many evoking procedures at normal T_b. Local application of aconitine, administration of $CaCl_2$ during K^+-free perfusion, procaine injection after adrenaline administration, and ligation of left descending coronary artery all failed to induce fibrillation in hibernators[37]. Although electrical stimulation during vulnerable period could produce ventricular fibrillation in a few hedgehogs, higher stimulus strength was needed[37].

Resistance against metabolic diseases

For surviving the long hibernation season without feeding, some hibernators store a massive amount of body fat as a fuel of hibernation in advance. Insulin resistance and hyperinsulinemia were reported to facilitate fat storing during the fattening period and be reversible during hibernation period[38]. The rapid and dramatic increase of body fat mass generally lead to the metabolic diseases, such as diabetes mellitus and atherosclerosis in laboratory rodents[39]; however, no atherosclerotic changes were found despite highly elevated plasma lipids in bear and ground squirrels[40-41]. Recently, the candidate noncoding *cis* elements that regulates hibernator fattening were identified by comparative phylogenomics[42]. The reversible insulin resistance and artery protective strategies provide clinical insights into the metabolic diseases.

Resistance against osteoporosis and muscle atrophy

The hibernators undergo about 6-month fasting and immobility during hibernation season. It generally increases the risk of osteoporosis and muscle disuse-atrophy in human. However, several hibernating species are able to prevent muscle atrophy and bone loss during prolonged hibernation season[43-47].

The above studies indicate that hibernating mammals can be used as a natural model for studying a wide spectrum of medical problems[48]. It is proposed that the hibernating phenotypes are resultant from differential expression of genes that are common to all mammalian species[2], although lineage-specific genes may also play a role in hibernation. Recently, the genomes of several hibernating spices have been sequenced, supporting that hibernators and non-hibernators share the major biological principles of signaling and regulation, and the mechanisms involved in hibernators may be effective in regulating human function. Therefore, detailed understanding of molecular

and genetic mechanisms of the stress resistance abilities of hibernating mammals will thus have intriguing medical implications.

Conflict of interests

All authors declare no competing financial interest.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (91854209, 31630035) , the Chinese Institute for Brain Research(2020-NKX-XM-09), and China Postdoctoral Science Foundation Grant(2019M660308).

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